

# Dual Pathway Inhibition for Vascular Protection in Patients with Atherosclerotic Disease: Rationale and Review of the Evidence

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## Abstract

Despite advances in secondary prevention strategies in patients with cardiovascular disease, the residual risk of recurrent atherothrombotic events remains high. Dual-antiplatelet therapy is the standard of care for secondary prevention in patients with acute coronary syndrome (ACS), whereas single antiplatelet therapy, generally with aspirin, is the standard of care for secondary prevention in stable patients with coronary artery disease (CAD), peripheral artery disease (PAD), or cerebrovascular disease. However, atherosclerotic plaque disruption not only triggers platelet activation but also results in thrombin generation because of tissue factor exposure. Therefore, blocking both pathways by combining antiplatelet therapy with an anticoagulant, or dual pathway inhibition (DPI), has the potential to be more effective than inhibiting either pathway alone. The benefit of DPI has been demonstrated in the ATLAS ACS 2-TIMI 51, COMPASS, and VOYAGER PAD trials, where the combination of rivaroxaban vascular dose (2.5 mg twice daily) plus aspirin significantly reduced the risk of atherothrombotic events compared with aspirin across a broad range of patients, including those with recent ACS, those with chronic CAD and/or PAD, and patients with PAD who have undergone peripheral revascularization. This article provides the rationale for this regimen in more detail, including why the DPI regimen with the rivaroxaban vascular dose was developed for vascular protection in a broad spectrum of patients with atherosclerotic disease.

## Keywords

- ▶ coronary artery disease
- ▶ dual pathway inhibition
- ▶ nonvitamin K antagonist oral anticoagulants
- ▶ peripheral artery disease
- ▶ rivaroxaban

## Introduction

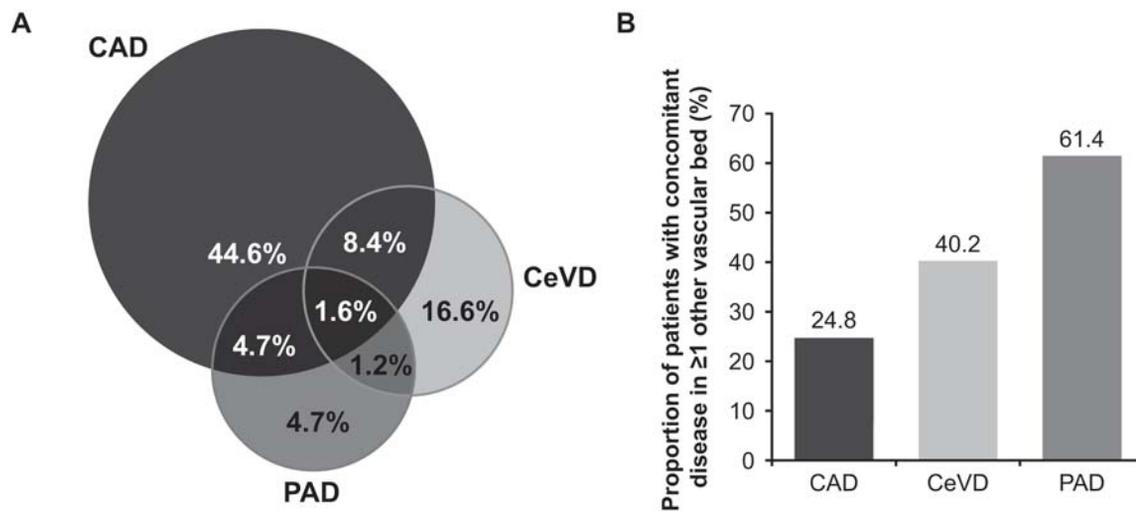
Atherosclerosis is a systemic disease that can affect the coronary, cerebral, or peripheral arteries.<sup>1</sup> Atherosclerotic plaques usually appear early in life, but only become symptomatic when there is vascular occlusion by expanding plaques or when

unstable plaques rupture and there is superimposed thrombosis.<sup>2,3</sup> Clinically, atherosclerosis manifests as cardiovascular disease (CVD), which is the leading cause of mortality and morbidity worldwide, and includes coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease (CeVD).<sup>2,4–7</sup> Many patients with atherosclerosis have

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**Fig. 1** Prevalence of polyvascular disease in the REACH registry.<sup>8</sup> (A) Proportion of patients of the total REACH population ( $N = 67,888$ ) with polyvascular disease. (B) Proportion of patients with coronary artery disease (CAD), cerebrovascular disease (CeVD), and peripheral artery disease (PAD) who have concomitant disease in  $\geq 1$  other vascular bed.

polyvascular involvement, with symptoms occurring in more than one vascular bed.<sup>8</sup> In the global Reduction of Atherothrombosis for Continued Health (REACH) registry, 15.9% of patients with symptomatic atherothrombotic disease had polyvascular involvement; 8.4% of these patients had CAD and CeVD, 4.7% had CAD and PAD, 1.2% had CeVD and PAD, and 1.6% had CAD, CeVD, and PAD ( $\rightarrow$  Fig. 1).<sup>8</sup> The risk of fatal and nonfatal adverse cardiovascular (CV) events increased as a function of the number of symptomatic disease locations,<sup>9,10</sup> emphasizing the importance of secondary CV prevention, particularly in patients with polyvascular disease.<sup>1,11</sup>

Antiplatelet therapy has been the mainstay of CV prevention in patients with CVD.<sup>12–16</sup> The focus on antiplatelet strategies reflects the fact that arterial thrombi, which form under high shear conditions, are rich in platelets and contain less fibrin than venous thrombi, which form where blood flow is sluggish.<sup>17</sup> Single or dual-antiplatelet therapy (DAPT) is used to reduce the risk of atherothrombotic events in patients with CVD. Single antiplatelet therapy usually involves the administration of aspirin or clopidogrel, whereas DAPT combines aspirin with a P2Y<sub>12</sub> inhibitor, such as clopidogrel, ticagrelor, or prasugrel.<sup>12–16</sup> DAPT is the standard of care (SOC) for secondary prevention in patients with acute coronary syndrome (ACS),<sup>12–15,18</sup> whereas single antiplatelet therapy is recommended for patients with symptomatic PAD or chronic CAD.<sup>11,16,19</sup> The recently published European Society of Cardiology guidelines on chronic coronary syndromes (CCS) now recommend the addition of a second antithrombotic drug to aspirin for long-term secondary prevention in patients with a high risk of ischemic events and without a high risk of bleeding.<sup>20</sup> Despite improvements in SOC and guideline recommendations for secondary prevention in patients with CAD and PAD, the residual risk of CV events remains high in such patients, ranging from approximately 15 to 30% at 3 years.<sup>21,22</sup> Therefore, more effective antithrombotic strategies are needed.

Atherothrombotic events are caused by disruption or erosion of atherosclerotic plaques and superimposed thrombosis.<sup>23,24</sup> Plaque disruption results in thrombus formation via the concomitant activation of platelets and coagulation.<sup>17,23</sup> Consequently, antithrombotic strategies that only focus on platelet inhibition may not fully suppress recurrent atherothrombotic events. This observation prompted the investigation of dual pathway inhibition (DPI) strategies, where an antiplatelet agent such as aspirin is combined with an anticoagulant.

The first phase 3 trial to investigate the efficacy and safety of DPI in patients with CVD was the Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome (ATLAS ACS 2-TIMI 51) trial. This trial demonstrated that the addition of rivaroxaban (2.5 or 5 mg twice daily) to a background of single antiplatelet therapy (low-dose aspirin) or DAPT (aspirin plus a P2Y<sub>12</sub> inhibitor) reduced atherothrombotic risk in patients with a recent ACS compared with antiplatelet therapy alone. Although DPI was associated with an increased risk of major bleeding and intracranial hemorrhage (ICH), there was no increase in the risk of fatal bleeding.<sup>25</sup> This led to the regulatory approval of DPI in this setting in some countries.<sup>26–28</sup>

More recently, the Cardiovascular Outcomes for People Using Anticoagulation StrategieS (COMPASS) trial showed that this benefit of DPI extended into patients with chronic CAD or PAD. The combination of rivaroxaban 2.5 mg twice daily plus aspirin, but not rivaroxaban 5 mg twice daily alone, was shown to be more effective than aspirin alone in reducing the risk of major adverse CV events (MACE) in patients with chronic CAD or PAD. Combination therapy was again associated with an increased risk of major bleeding, but there was no significant increase in the risk of fatal bleeding or ICH.<sup>29–31</sup> These results led to the widespread approval of rivaroxaban 2.5 mg twice daily plus aspirin for patients with chronic CAD or PAD.<sup>26–28</sup>

Finally, the recent Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease (VOYAGER PAD) trial extended the evidence base for DPI to include patients with symptomatic PAD undergoing lower extremity revascularization. Patients treated with rivaroxaban 2.5 mg twice daily plus aspirin had a 15% reduction in the risk of the composite outcome of myocardial infarction (MI), ischemic stroke, CV death, acute limb ischemia (ALI), and major amputation of vascular etiology.<sup>32</sup> The risk of the primary safety outcome of Thrombolysis In Myocardial Infarction (TIMI) major bleeding was not significantly different with DPI versus aspirin in the VOYAGER PAD study.<sup>32</sup>

Although the results of these trials highlight the value of DPI in a broad range of patients, the rationale for DPI needs to be fully understood by physicians in order to optimize the benefits of this treatment. After reviewing the results of the ATLAS ACS 2-TIMI 51, COMPASS, and VOYAGER PAD trials in more detail, this article addresses four commonly asked questions about DPI with rivaroxaban 2.5 mg twice daily plus aspirin:

1. What is the rationale for combining an antiplatelet agent with an anticoagulant?
2. Why should a lower dose of rivaroxaban be used rather than the higher dose that is used for stroke prevention in patients with atrial fibrillation (AF) or for venous thromboembolism (VTE) treatment?
3. Why should twice-daily dosing with rivaroxaban 2.5 mg be used rather than once-daily dosing?
4. Which patients might benefit most from the dual pathway regimen?

### Evidence Base for Dual Pathway Inhibition in Patients with Cardiovascular Disease

The phase 3 ATLAS ACS 2-TIMI 51 trial showed that adjunctive therapy with rivaroxaban (2.5 or 5 mg twice daily) on a background of antiplatelet therapy significantly reduced the primary efficacy endpoint, defined as a composite of CV death, MI, or stroke, in more than 15,000 patients with a recent ACS, compared with placebo (8.9% vs. 10.7%, hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.74–0.96;  $p = 0.008$ ). This benefit with rivaroxaban was consistent among subgroups except for patients with a history of stroke or transient ischemic attack (HR, 1.57; 95% CI, 0.75–3.31).<sup>25</sup>

More recently, the phase 3 COMPASS trial showed that the benefit of DPI extended to patients with chronic CAD or PAD. Thus, DPI with rivaroxaban 2.5 mg twice daily plus aspirin, but not monotherapy with rivaroxaban 5 mg twice daily alone, was superior to aspirin alone for the prevention of MACE, defined as the composite of CV death, MI, or stroke, in a population of 27,395 patients with chronic CAD or PAD.<sup>29</sup> MACE occurred in 4.1% of patients receiving rivaroxaban 2.5 mg twice daily plus aspirin, in 5.4% of those receiving aspirin alone, and in 4.9% of those receiving rivaroxaban alone (rivaroxaban plus aspirin vs. aspirin alone: absolute risk reduction, 1.3%; number needed to treat, 77; HR, 0.76; 95% CI, 0.66–0.86;  $p < 0.001$ ; rivaroxaban alone vs. aspirin

alone: absolute risk reduction, 0.5%; number needed to treat, 200; HR, 0.90; 95% CI, 0.79–1.03;  $p = 0.12$ ).<sup>29</sup> Compared with aspirin alone, the combination of rivaroxaban 2.5 mg twice daily plus aspirin also reduced the risk of stroke by 42% (HR, 0.58; 95% CI, 0.44–0.76;  $p < 0.0001$ ).<sup>33</sup> The decreased risk of stroke was primarily driven by a reduction in the risk of ischemic stroke (HR, 0.51; 95% CI, 0.38–0.68;  $p < 0.0001$ ) with relative risk reductions of 70 and 60% for cardioembolic stroke and embolic stroke of undetermined source, respectively.<sup>33,34</sup> Rivaroxaban 2.5 mg twice daily in combination with aspirin was also shown to reduce MACE and major adverse limb events compared with aspirin or rivaroxaban alone in patients with PAD, including those with carotid artery disease (defined as previous carotid artery revascularization or asymptomatic carotid artery stenosis of at least 50%).<sup>31</sup> Thus, a reduction in the risk of MACE and major adverse limb events was achieved with the combination of rivaroxaban vascular dose and aspirin, but not with low-dose rivaroxaban alone.<sup>29</sup>

Building on the evidence for the utility of DPI with rivaroxaban 2.5 mg twice daily plus aspirin are the recent results from the phase 3 VOYAGER PAD trial, which investigated this treatment strategy in patients with symptomatic PAD undergoing lower extremity revascularization. Compared with aspirin alone, rivaroxaban 2.5 mg twice daily plus aspirin significantly reduced the 3-year incidence of the composite of MI, ischemic stroke, CV death, ALI, and major amputation for vascular causes compared with aspirin (17.3% with DPI vs. 19.9% with aspirin, HR, 0.85; 95% CI, 0.76–0.96;  $p = 0.009$ ). This broad benefit was seen early, with separation of the Kaplan–Meier curves at 3 months, which was maintained over time and was consistent across major subgroups. In addition, the incidence of the secondary outcome of unplanned index limb revascularization for recurrent ischemia was significantly lower with rivaroxaban 2.5 mg twice daily plus aspirin compared with aspirin alone (HR, 0.88; 95% CI, 0.79–0.99;  $p = 0.03$ ), while death from any cause did not differ between treatment groups (HR, 1.08; 95% CI, 0.92–1.27;  $p = 0.34$ ).<sup>32</sup> Overall, these findings complement the results of the ATLAS ACS 2-TIMI 51 and COMPASS trials and provide further support for the use of DPI with rivaroxaban 2.5 mg twice daily plus aspirin in patients with CVD.

As expected when an anticoagulant is added to an antiplatelet agent, the risk of major bleeding was increased with rivaroxaban plus aspirin compared with aspirin alone in both the ATLAS ACS 2-TIMI 51 and COMPASS trials, although there was no increase in the risk of fatal bleeding.<sup>25,29</sup> In the ATLAS ACS 2-TIMI 51 trial, the rate of TIMI major bleeding, not related to coronary artery bypass grafting, was higher in patients receiving rivaroxaban 2.5 or 5 mg twice daily compared with placebo (2.1% vs. 0.6%, HR, 3.96; 95% CI, 2.46–6.38;  $p < 0.001$ ). Rates of TIMI minor bleeding and ICH were also increased with rivaroxaban compared with placebo (1.3% vs. 0.5%,  $p = 0.003$  and 0.6% vs. 0.2%,  $p = 0.009$ , respectively), but the rate of fatal bleeding did not significantly differ between the treatment groups (0.3% vs. 0.2%,  $p = 0.66$ ).<sup>25</sup> Furthermore, the rates of major bleeding were

lower with rivaroxaban 2.5 mg twice daily than with the 5 mg twice daily dose (1.8% and 2.4%, respectively).<sup>25</sup>

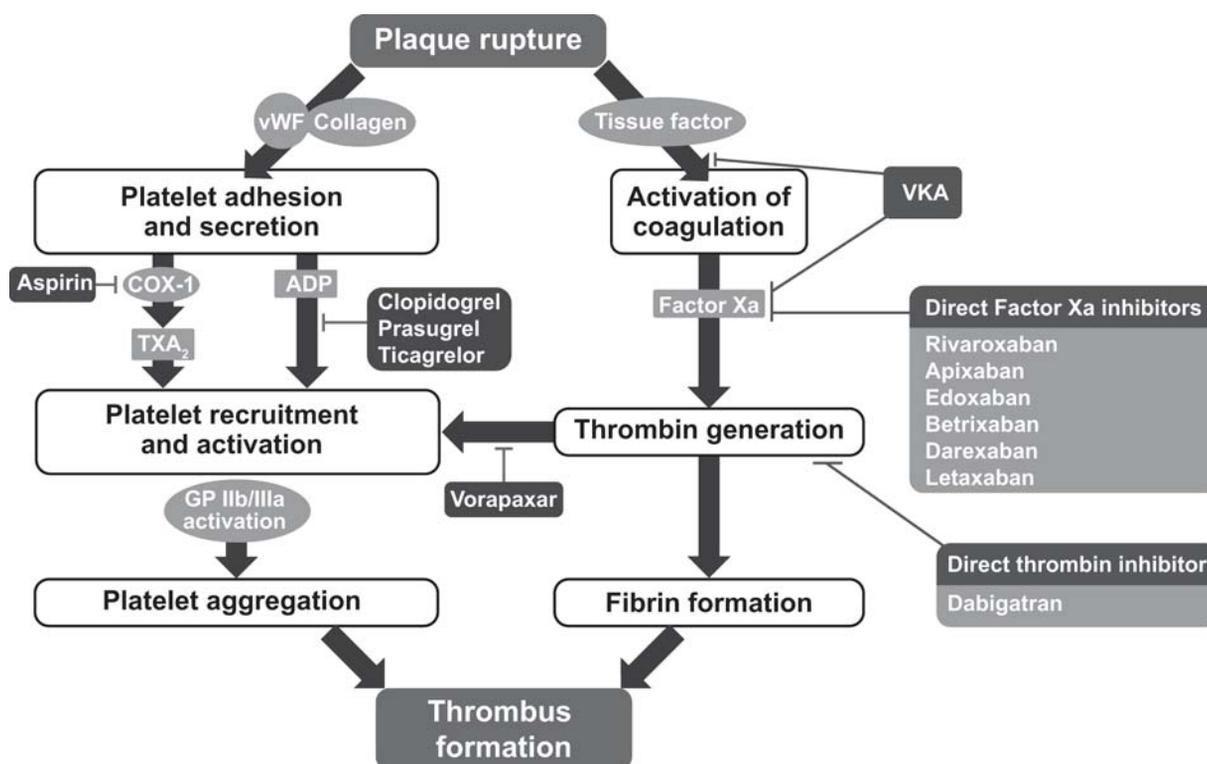
Results from the COMPASS trial reported major bleeding in 3.1% of patients receiving rivaroxaban 2.5 mg twice daily plus aspirin versus 1.9% of patients receiving aspirin alone (absolute risk increase, 1.2%; number needed to harm, 83; HR, 1.70; 95% CI, 1.40–2.05;  $p < 0.001$ ).<sup>29</sup> The rates of fatal bleeding were 0.2 and 0.1% with DPI and aspirin alone, respectively (HR, 1.49; 95% CI, 0.67–3.33;  $p = 0.32$ ), whereas the rates of ICH were 0.2% in both groups (HR, 1.10; 95% CI, 0.59–2.04;  $p = 0.77$ ).<sup>29</sup> Therefore, even though combination therapy resulted in an increased risk of major bleeding, the risk of fatal or critical organ bleeding (including ICH) was not increased compared with aspirin alone.<sup>31</sup> In addition, the risk of the composite net clinical benefit outcome of CV death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ was found to be lower with rivaroxaban 2.5 mg twice daily plus aspirin compared with aspirin alone (HR, 0.80; 95% CI, 0.70–0.91;  $p < 0.001$ ), indicating an improved benefit–risk profile for the combination therapy compared with aspirin alone.<sup>29</sup>

In the VOYAGER PAD trial, the 3-year rate of TIMI major bleeding in patients treated with rivaroxaban 2.5 mg twice daily plus aspirin was not significantly different compared with patients receiving aspirin alone (2.65% vs. 1.87%, HR, 1.43; 95% CI, 0.97–2.10;  $p = 0.07$ ). However, using the International Society on Thrombosis and Haemostasis criteria, the rate of major bleeding was significantly higher in patients treated with rivaroxaban 2.5 mg twice daily plus aspirin compared with aspirin alone (5.94% vs. 4.06%, HR, 1.42; 95% CI, 1.10–1.84;

$p = 0.007$ ). There was no excess in ICH with rivaroxaban 2.5 mg twice daily plus aspirin compared with aspirin alone (0.60% vs. 0.90%, HR, 0.78; 95% CI, 0.38–1.61), and the rate of fatal bleeding was 0.21% in both groups.<sup>32</sup>

## What Is the Rationale for Combining an Antiplatelet Agent with an Anticoagulant?

The progression from early atherosclerotic lesions to rupture-prone plaques involves complex interplay between coagulation and inflammation pathways.<sup>3,24,35,36</sup> Rupture of atherosclerotic plaques induces simultaneous activation of platelets and of the coagulation cascade (→ Fig. 2), resulting in the formation of superimposed thrombi, which are mainly composed of platelets.<sup>17</sup> Platelets adhere to collagen and von Willebrand factor (vWF) exposed at sites of plaque rupture.<sup>17</sup> Adherent platelets become activated and release adenosine diphosphate and thromboxane A<sub>2</sub>, platelet agonists that activate ambient platelets, thereby recruiting them to the site of injury. Platelet activation leads to the activation of glycoprotein (GP) IIb/IIIa on the surface of platelets.<sup>17</sup> Binding of fibrinogen to activated GPIIb/IIIa on adjacent platelets bridges them together, which leads to platelet aggregation. Under high shear conditions, unfolded vWF can also contribute to this bridging process.<sup>17</sup> Concomitant with platelet activation and aggregation, plaque rupture exposes tissue factor, which initiates the coagulation cascade and triggers thrombin generation and fibrin formation. Fibrin monomers polymerize into strands that tie the platelet aggregates together and stabilize the platelet-rich thrombus.<sup>36</sup>



**Fig. 2** Pathways for thrombus formation and targets for oral antithrombotic agents. The dual pathway of thrombus formation comprises platelet activation/aggregation and coagulation. Antiplatelet agents and anticoagulants target the respective pathways at different sites. ADP, adenosine diphosphate; COX, cyclooxygenase; GP, glycoprotein; TXA<sub>2</sub>, thromboxane A<sub>2</sub>; VKA, vitamin K antagonist; vWF, von Willebrand factor.

The coagulation and platelet pathways intersect at several sites (►Fig. 2). For example, thrombin is not only an important mediator of the coagulation cascade but also acts as a potent platelet agonist that induces platelet activation and aggregation via activation of protease-activated receptors (PARs) PAR-1 and PAR-4 on the platelet surface.<sup>17,37</sup> Recent data suggest that factor Xa, which converts prothrombin to thrombin, may also activate PAR-1.<sup>37–39</sup> In turn, platelets play an important part in amplifying thrombin generation, because the intrinsic tenase and prothrombinase complexes, which mediate the generation of factor Xa and thrombin, respectively, assemble on the activated platelet surface.<sup>17,37</sup>

Because of the coordinated, synergistic involvement of platelets and coagulation in atherothrombosis, treatment strategies targeting both fibrin generation and platelet activation, termed “DPI”, are likely to be more effective than those inhibiting only one of these two pathways. This concept is supported by the observations that: (1) despite SOC therapy, markers of coagulation system activation (e.g., fibrinopeptide A, prothrombin fragment F1.2, and D-dimer), and thrombin generation remain elevated for months after ACS<sup>40–42</sup>; (2) preclinical studies show that combining an anticoagulant with single antiplatelet therapy or DAPT provides additive or synergistic effects in *in vitro* assays and enhances antithrombotic efficacy in animal models<sup>43,44</sup>; and (3) low doses of rivaroxaban reduce thrombin generation in patients on antiplatelet therapy.<sup>45</sup>

As mentioned above, antiplatelet therapy is the SOC for secondary prevention of CV events in patients with CVD. However, despite improvements in secondary prevention strategies, such as DAPT, the risk of CV events remains high. Trials comparing DAPT consisting of aspirin plus a P2Y<sub>12</sub> inhibitor (e.g., clopidogrel or ticagrelor) with aspirin alone revealed that more intensified platelet inhibition resulted in a greater reduction in atherothrombotic risk but also increased the risk of major bleeding.<sup>46–48</sup> For example, in the CHARISMA trial, which compared clopidogrel plus aspirin with aspirin alone in patients with documented atherosclerotic disease or multiple atherothrombotic risk factors, there was no significant difference in the rate of CV events with DAPT, but DAPT was associated with an increased risk of bleeding.<sup>46</sup> In the subgroup of patients with documented prior MI, stroke, or symptomatic PAD, the DAPT regimen had a significant benefit, but it increased the risk of moderate, although not severe, bleeding.<sup>47</sup> In the PEGASUS-TIMI 54 trial, ticagrelor plus aspirin was associated with a significant reduction in the risk of MACE and an increased risk of major bleeding in patients with a history of MI 1 to 3 years previously.<sup>49</sup> Finally, the EUCLID trial revealed no benefit of the more potent P2Y<sub>12</sub> antagonist ticagrelor over clopidogrel for secondary prevention in patients with symptomatic PAD, although the risk of major bleeding was similar between treatment groups.<sup>50</sup>

Vorapaxar, a PAR-1 antagonist that targets a different pathway of platelet activation than aspirin or the P2Y<sub>12</sub> inhibitors, has also been evaluated for secondary prevention in patients with CVD.<sup>51–53</sup> When added on top of SOC in patients with ACS,<sup>53</sup> or those with a history of MI, ischemic stroke, or PAD,<sup>51,52</sup> vorapaxar reduced the incidence of CV events versus placebo, but was associated with an increased

risk of serious bleeding events.<sup>51–53</sup> Thus, the limited success of intensified antiplatelet regimens suggested that another strategy was needed to reduce the residual atherothrombotic risk in patients with chronic CAD or PAD.

A new and more effective approach may be to target thrombin generation in addition to platelet activation. Thus, such a DPI regimen would combine an antiplatelet agent, such as aspirin, with an oral anticoagulant (OAC) that targets fibrin formation, such as a vitamin K antagonist (VKA) (►Fig. 2; ►Table 1). This concept was confirmed in phase 3 trials such as Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2)<sup>54</sup> and Warfarin-Aspirin Reinfarction Study II (WARIS II),<sup>55</sup> which assessed the efficacy and safety of aspirin, a VKA, or a combination of both in patients with recent ACS. When the VKA was dosed to produce a therapeutic international normalized ratio of 2 to 3, VKA alone or combined with aspirin was shown to be more effective in reducing the risk of CV events than antiplatelet therapy with aspirin alone in patients with ACS, but also resulted in an increased risk of bleeding.<sup>54,55</sup> Attempts to reduce the risk of bleeding by lowering the intensity of VKA therapy (target international normalized ratio of 1.5–2.5) were unsuccessful, because the efficacy in decreasing atherothrombotic events and all-cause mortality was also reduced.<sup>56</sup> Another disadvantage of VKAs is that their use is inconvenient, because of the large within- and between-patient variability in dose response, thus requiring frequent coagulation monitoring and dose adjustment, as well as careful avoidance of potential food–drug and drug–drug interactions.<sup>57,58</sup>

Non-VKA OACs (NOACs) attenuate thrombin generation and fibrin production by inhibiting factor Xa or thrombin, and therefore also have the potential to be used as part of a DPI strategy in combination with an antiplatelet agent (►Fig. 2). As mentioned above, it has also been suggested that concomitant administration of NOACs and antiplatelet agents synergistically enhances the antithrombotic effect.<sup>59–61</sup> In contrast to VKAs, NOACs do not require routine monitoring, have fewer drug–drug interactions, and are unaffected by changes in dietary intake of vitamin K.<sup>27,58,62,63</sup> In addition, NOACs have been shown to have an improved benefit–risk profile compared with VKAs, such as warfarin, in patients with AF or VTE.<sup>64,65</sup>

Clinical trials have been conducted to assess the efficacy and safety of NOACs in combination with aspirin in patients with acute or chronic CVD as part of a DPI regimen (►Table 1).<sup>66</sup> In the phase 2 RandomizEd Dabigatran Etxilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel: Multi-centre, Prospective, Placebo Controlled, Cohort Dose Escalation Study (RE-DEEM) trial, dabigatran (110–150 mg twice daily) added to DAPT significantly reduced coagulation activity in patients with a recent MI, but was associated with a dose-dependent increase in bleeding events.<sup>67</sup> In the phase 3 Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) trial, apixaban (5 mg twice daily) was compared with placebo on top of background therapy that included aspirin with or without a P2Y<sub>12</sub> receptor antagonist. The trial was terminated early, because

**Table 1** Trials investigating combination therapies of antiplatelet and oral anticoagulant agents in patients with CAD and PAD

Drug class	Trial	Patient population	Treatment arms	Key outcomes
Post-ACS setting				
VKA plus antiplatelet	ASPECT-2 <sup>54</sup>	Patients with acute MI or unstable angina (N = 999)	Coumadin plus aspirin vs. aspirin alone vs. coumadin alone	<ul style="list-style-type: none"> <li>Coumadin combined with aspirin or given alone was superior to aspirin alone in reducing CV events and death but was associated with a higher risk of bleeding</li> </ul>
	WARIS II <sup>55</sup>	Patients with acute MI (N = 3,630)	Warfarin plus aspirin vs. aspirin alone vs. warfarin alone	<ul style="list-style-type: none"> <li>Warfarin combined with aspirin or given alone was more effective than aspirin alone in reducing the incidence of CV events but was associated with a higher risk of bleeding</li> </ul>
NOAC plus antiplatelet	RE-DEEM <sup>67</sup>	Patients with recent NSTEMI or STEMI (N = 1,861)	Dabigatran 50 mg, 75 mg, 110 mg, or 150 mg bid plus DAPT vs. placebo plus DAPT	<ul style="list-style-type: none"> <li>Dabigatran added to DAPT resulted in a dose-dependent increase in bleeding events and significantly reduced coagulation activity in patients with a recent MI</li> </ul>
	APPRaise-2 <sup>66</sup>	Patients with recent unstable angina, NSTEMI, or STEMI (N = 7,392)	Apixaban 5 mg bid plus standard antiplatelet therapy vs. placebo plus standard antiplatelet therapy	<ul style="list-style-type: none"> <li>Apixaban added to standard antiplatelet therapy increased the risk of major bleeding without a significant reduction in recurrent ischemic events (trial was terminated prematurely)</li> </ul>
	ATLAS ACS TIMI 46 <sup>69</sup>	Patients with recent unstable angina, NSTEMI, or STEMI (N = 3,491 patients)	Rivaroxaban 5 mg, 10 mg, 15 mg, or 20 mg bid plus standard antiplatelet therapy vs. placebo plus standard antiplatelet therapy	<ul style="list-style-type: none"> <li>Rivaroxaban added to standard antiplatelet therapy resulted in a dose-dependent increase in bleeding events and a reduction in ischemic events, even with the lowest dose</li> </ul>
	ATLAS ACS 2-TIMI 51 <sup>25</sup>	Patients with recent unstable angina, NSTEMI, or STEMI (N = 15,526 patients)	Rivaroxaban 2.5 mg bid plus standard antiplatelet therapy vs. rivaroxaban 5 mg bid plus standard antiplatelet therapy vs. placebo plus standard antiplatelet therapy	<ul style="list-style-type: none"> <li>Both doses of rivaroxaban reduced the risk of the composite end point of CV death, MI, or stroke, with an increase in major bleeding and ICH but not fatal bleeding</li> <li>The 2.5 mg bid dose was associated with fewer fatal bleeding events than the 5 mg bid dose</li> </ul>
	GEMINI ACS 1 <sup>71</sup>	Patients with unstable angina, NSTEMI or STEMI (N = 3,037)	Rivaroxaban 2.5 mg bid plus P2Y <sub>12</sub> inhibitor vs. aspirin plus P2Y <sub>12</sub> inhibitor	<ul style="list-style-type: none"> <li>Rivaroxaban 2.5 mg bid plus P2Y<sub>12</sub> inhibitor resulted in a similar risk of clinically significant bleeding as aspirin plus P2Y<sub>12</sub> inhibitor</li> </ul>
Chronic CAD and/or PAD				
NOAC plus antiplatelet	COMPASS <sup>29</sup>	Patients with chronic CAD and PAD (N = 27,395)	Rivaroxaban 2.5 mg bid plus aspirin vs. rivaroxaban 5 mg bid vs. aspirin	<ul style="list-style-type: none"> <li>Rivaroxaban 2.5 mg bid plus aspirin significantly reduced the risk of CV events compared with aspirin or rivaroxaban alone and increased the risk of major bleeding; however, fatal bleeding or ICH were not significantly increased</li> </ul>
Symptomatic PAD following peripheral revascularization				
NOAC plus antiplatelet	VOYAGER PAD <sup>32,93</sup>	Patients with symptomatic PAD and recent lower extremity revascularization	Rivaroxaban 2.5 mg bid plus aspirin vs. aspirin	<ul style="list-style-type: none"> <li>Rivaroxaban 2.5 mg bid plus aspirin significantly reduced the risk of major adverse cardiovascular and ischemic limb events and did not significantly increase the risk of TIMI major bleeding versus aspirin</li> </ul>

Abbreviations: ACS, acute coronary syndrome; bid, twice daily; CAD, coronary artery disease; CV, cardiovascular; DAPT, dual-antiplatelet therapy; ICH, intracranial hemorrhage; MI, myocardial infarction; NOAC, nonvitamin K antagonist oral anticoagulant; NSTEMI, non-ST segment elevation myocardial infarction; PAD, peripheral artery disease; STEMI, ST segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; VKA, vitamin K antagonist.

apixaban (5 mg twice daily) did not significantly reduce the risk of ischemic events in patients with recent ACS, but led to an increase in major bleeding, including fatal bleeding and ICH.<sup>66</sup> This full-dose apixaban regimen, which is similar to the one used as sole therapy for stroke prevention in the majority of patients with AF,<sup>66,68</sup> was chosen based on phase 2 data from APPRAISE suggesting that apixaban doses of 2.5 mg twice daily or 10 mg once daily might have a favorable benefit–risk profile.

In the case of rivaroxaban, it was the lower-dose regimens that offered the best balance between efficacy and safety in the

phase 2 ATLAS ACS-TIMI 46 trial. This trial investigated total daily doses of rivaroxaban ranging from 5 to 20 mg administered once daily or twice daily in patients with recent ACS who were also receiving aspirin (75–100 mg once daily) with or without a thienopyridine.<sup>69</sup> The risk of bleeding increased with higher doses of rivaroxaban, but lower doses were sufficient to reduce the risk of ischemic events.<sup>69</sup> The two doses of rivaroxaban (2.5 and 5 mg twice daily) identified in the ATLAS ACS-TIMI 46 trial were assessed for reducing the risk of CV events in patients with recent ACS in the phase 3 ATLAS ACS 2-TIMI 51 trial.<sup>25</sup> The combination of rivaroxaban 2.5 mg twice daily or

rivaroxaban 5 mg twice daily with background therapy that included DAPT with aspirin and a thienopyridine (predominantly clopidogrel) significantly reduced the risk of MACE.<sup>25</sup> Although the risks of major bleeding and ICH were increased, there was no difference in the risk of fatal bleeding compared with background therapy.<sup>25</sup> While the 5 mg twice daily dose was associated with a reduction in all-cause mortality, the lower 2.5 mg twice daily dose was associated with a decrease in both CV and all-cause mortality. The reason why CV mortality was reduced in the rivaroxaban 2.5 mg twice daily group but not in the 5 mg twice daily group is unclear, but it could reflect the higher rate of bleeding with the 5 mg twice daily dose.<sup>25</sup> In a subanalysis of the ATLAS ACS 2-TIMI 51 trial in stented patients with ACS treated with DAPT, rivaroxaban 2.5 mg twice daily also resulted in a reduction in stent thrombosis and mortality.<sup>70</sup> These results confirmed that DPI with a low dose of a NOAC and DAPT improves protection against CV events in patients with ACS who have elevated biomarkers. In addition, the Study to Compare the Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor Therapy in Participants With Acute Coronary Syndrome 1 (GEMINI ACS 1) trial demonstrated a similar risk of clinically significant bleeding with rivaroxaban 2.5 mg twice daily combined with a P2Y<sub>12</sub> inhibitor compared with aspirin and a P2Y<sub>12</sub> inhibitor for the treatment of patients with ACS,<sup>71</sup> further supporting the rationale for using this DPI regimen after ACS.

### Why Should a Lower Dose of Rivaroxaban Be Used Rather than the Higher Dose that is Used for Stroke Prevention in Patients with Atrial Fibrillation or for Venous Thromboembolism Treatment?

Rivaroxaban can be part of the treatment strategy to prevent ischemic events in patients with AF, VTE, and CVD, but the indications and dose recommendations differ among these patient populations (►Table 2).<sup>27,29,72</sup> The doses recom-

mended to reduce the risk of stroke in patients with AF and the risk of VTE are higher than that recommended for reducing the residual risk of CV events in patients with CVD who are concomitantly receiving antiplatelet therapy.<sup>27,29,72</sup> The different indications and dose recommendations can be explained by the different pathophysiology and therapeutic goals of the various conditions. Thrombi formed under low-shear stress conditions, as in venous thrombosis and in the low-flow environment of the left atrial appendage in AF, predominantly consist of fibrin,<sup>17,73</sup> justifying the use of anticoagulants for the prevention of cardioembolic stroke and for the prevention and treatment of VTE. In contrast, in atherothrombosis, the thrombi that form under high-shear conditions are platelet-rich but thrombin-driven, thus indicating the need for an anticoagulant in addition to antiplatelet treatments in patients with CVD.<sup>17,23,74</sup> Given the increased risk of bleeding when combining anticoagulant and antiplatelet therapies, it is essential to use the lowest effective dose of anticoagulant to minimize the risk of bleeding. Phase 2 and 3 trials showed that low-dose rivaroxaban combined with aspirin was effective in reducing CV events in patients with recent ACS and elevated biomarkers, with a satisfactory safety profile.<sup>25,27,69</sup> The rivaroxaban doses of 2.5 and 5 mg twice daily had the best balance between safety and efficacy in patients with recent ACS, and were therefore assessed in patients with stable CVD in the phase 3 COMPASS trial.<sup>25,29,69</sup>

### Why Should Twice-Daily Dosing with Rivaroxaban 2.5 mg Be Used Rather than Once-Daily Dosing?

Rivaroxaban is absorbed rapidly, with maximum plasma concentrations achieved 2 to 4 hours after oral administration and peak factor Xa inhibition occurring after approximately 3 hours.<sup>75-77</sup> Plasma concentrations of rivaroxaban increase in a dose-dependent manner and are closely correlated with the level of factor Xa inhibition, as well as prolongation of prothrombin time and activated partial thromboplastin

**Table 2** Dose recommendations for rivaroxaban for different indications

Indication <sup>a</sup>	Treatment regimens/dose recommendations
Prevention of atherothrombotic events in adult patients with CAD or PAD <sup>26,27</sup>	Rivaroxaban 2.5 mg bid coadministered with aspirin
Prevention of atherothrombotic events in adult patients after an ACS event with elevated biomarkers <sup>27</sup>	Rivaroxaban 2.5 mg bid coadministered with aspirin alone or with aspirin plus clopidogrel or ticlopidine
Prevention of stroke and systemic embolism in adult patients with nonvalvular AF <sup>26,27</sup>	Rivaroxaban 20 mg od <sup>b</sup>
Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery <sup>26,27</sup>	Rivaroxaban 10 mg od
Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults <sup>26,27</sup>	Rivaroxaban 15 mg bid Day 1–21 Rivaroxaban 20 mg bid Day 22 onwards Rivaroxaban 10 mg od or 20 mg od following completion of at least 6 mo therapy for DVT or PE

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; bid, twice daily; CAD, coronary artery disease; CV, cardiovascular; DVT, deep vein thrombosis; od, once daily; PAD, peripheral artery disease; PE, pulmonary embolism; VTE, venous thromboembolism.

<sup>a</sup>Please refer to label for exact wording.

<sup>b</sup>Rivaroxaban 15 mg od is recommended in patients with creatinine clearance  $\leq$  50 mL/min.

time.<sup>76,78</sup> The half-life of rivaroxaban is dose-dependent, as demonstrated in two phase 1 studies that compared the pharmacokinetics of 2.5 to 20 mg doses of rivaroxaban in healthy male subjects.<sup>79</sup> Whereas doses of 2.5 mg are eliminated from the plasma with a half-life of approximately 5 hours, the half-life of 10 or 20 mg doses is about twice as long.<sup>79</sup> Therefore, because of the 5-hour half-life of the rivaroxaban 2.5 mg dose, plasma levels at trough would be too low if that dose was administered once daily, which would compromise efficacy. Thus, a twice daily dosing regimen ensures that effective plasma levels are maintained throughout the day when rivaroxaban vascular doses are administered.

The longer half-life of rivaroxaban doses of 10 mg and above provides a rationale for the once daily treatment regimens used for patients with AF and for VTE treatment (20 mg), and for VTE prevention (10 mg).<sup>27</sup> The high-dose once daily regimen for patients with AF and VTE is based on phase 2b trials, in which once daily and twice daily dosing regimens had similar efficacy and safety profiles.<sup>80–82</sup> To minimize the risk of bleeding, the lowest effective dose was assessed further in phase 3 clinical trials and ultimately approved for use in the respective indications. In patients with CVD, total daily rivaroxaban doses of 5 or 10 mg were associated with less bleeding and similar efficacy compared with higher doses, as demonstrated in the phase 2 ATLAS ACS-TIMI 46 trial.<sup>69</sup> Based on the pharmacokinetic and pharmacodynamic profiles that suggest insufficient trough levels for once daily doses of rivaroxaban below 10 mg, a twice daily dosing regimen was selected.<sup>69,76</sup> Rivaroxaban 5 mg once daily is, therefore, not therapeutically equivalent to rivaroxaban 2.5 mg twice daily in patients with chronic CAD or PAD. To maintain a clinically effective concentration of rivaroxaban throughout the day, which is required for continuous protection against atherothrombotic events, it is important to use a twice daily regimen for these patients.

### Which Patients Might Benefit Most from the Dual Pathway Regimen?

Results from three phase 3 trials (ATLAS ACS 2-TIMI 51, COMPASS, and VOYAGER PAD), which included almost 50,000 patients in total, have established the utility of the DPI regimen in a broad range of patients, with subgroup analyses demonstrating consistent efficacy and safety results across major subgroups.<sup>25,29–32</sup> However, patient subgroups at the highest absolute risk were shown to experience the greatest absolute benefit with DPI therapy. A risk-stratification analysis of the COMPASS trial population demonstrated that patients with the highest baseline risk, including those with polyvascular disease, renal impairment (estimated glomerular filtration rate [eGFR] < 60 mL/min), and those with a history of heart failure or diabetes, particularly benefited from the COMPASS regimen, as reflected by their higher absolute risk reductions.<sup>83</sup>

Consistent with the COMPASS trial and the risk-stratification analysis, the 2019 European Society of Cardiology guidelines on CCS now recommend considering adding a second antithrombotic agent to aspirin for long-term secondary prevention in patients with a low bleeding risk who are at

high risk of ischemic events (i.e., those with diffuse multivessel CAD with at least one additional risk factor, such as diabetes that requires medication, recurrent MI, PAD, or chronic kidney disease with eGFR 15–59 mL/min).<sup>20</sup> This recommendation may also be considered for moderate-risk patients (i.e., those with multivessel/diffuse CAD and/or at least one other risk factor listed above, or heart failure).<sup>20</sup> Antithrombotic agents that can be added to aspirin include the P2Y<sub>12</sub> inhibitors clopidogrel, prasugrel or ticagrelor, and rivaroxaban, which is the only anticoagulant recommended for long-term secondary prevention in patients with CCS.<sup>20</sup>

The results of the COMPASS trial indicate that DPI improves CV outcomes and overall mortality in a broad patient population. The guidelines recommend considering DPI in patients > 1 year post-MI or with multivessel CAD, whereas DAPT is primarily recommended for up to 1 year post-MI, although it may be continued longer in patients at low risk for bleeding and high risk for recurrent ischemic events.<sup>20</sup> As expected with intensified antithrombotic therapies, both strategies—DPI and DAPT—are associated with an increased risk of bleeding, which is acknowledged in the new guidelines. Therefore, a second antithrombotic agent is only recommended in patients who are not at high risk of bleeding (defined as a history of ICH; ischemic stroke or other intracranial pathology; recent gastrointestinal [GI] bleeding; anemia due to possible GI blood loss or other GI pathology associated with increased bleeding risk; liver failure; bleeding diathesis or coagulopathy; extreme old age or frailty; or renal failure requiring dialysis or eGFR < 15 mL/min/m<sup>2</sup>).<sup>20</sup> A recent review proposed a practical algorithm for selecting an antithrombotic strategy in patients with CCS.<sup>84</sup>

There are no head-to-head comparisons between DAPT and DPI in patients with CVD. Therefore, the choice of treatment needs to be individualized, based on balancing of the risks of ischemic events and bleeding. An analysis of data from the REACH registry showed that, while the risk of ischemic events increases with accumulating risk factors, the risk of serious bleeding increases at a much lower rate in a COMPASS-eligible population.<sup>85</sup> Thus, patients with high ischemic risk appear to have a more favorable benefit-risk profile than those with a lower ischemic risk, suggesting that these patients may be good candidates for DPI.

Recently published treatment strategies suggest the use of DPI in patients with chronic vascular disease and additional high-risk factors,<sup>86–88</sup> and in patients with symptomatic PAD.<sup>89</sup> However, it is important to keep in mind that the management of patients with chronic CVD not only includes antithrombotic therapy but also lifestyle modifications and pharmacological interventions targeting other aspects of CV risk such as dyslipidemia, diabetes, and hypertension.<sup>20</sup> The patients enrolled in the COMPASS trial were already receiving a high level of SOC, suggesting that DPI is beneficial even in well-managed patients.

### Conclusion and Future Directions

DPI aims to reduce the risk of residual CV events by targeting both of the pathways involved in atherothrombosis: platelet aggregation and fibrin formation. In the ATLAS ACS 2-TIMI

51, COMPASS, and VOYAGER PAD trials, a combination of rivaroxaban vascular dose (2.5 mg twice daily) plus aspirin significantly reduced the risk of atherothrombotic events compared with aspirin in patients with ACS, chronic CAD, or PAD, including those with carotid artery disease, and in patients with symptomatic PAD undergoing lower extremity revascularization. The efficacy of rivaroxaban vascular dose as part of the COMPASS regimen in patients with chronic CAD and PAD, in contrast to the high doses required for secondary CV prevention in patients with AF and VTE, can be explained by underlying differences in the pathophysiology of these conditions and the synergistic effects achievable with DPI. Whereas higher doses of rivaroxaban are needed to target the fibrin-rich thrombi formed in AF and VTE, the rivaroxaban vascular dose as part of the dual inhibition strategy in combination with an antiplatelet agent is more likely to affect the formation of platelet-rich thrombi than anticoagulation alone in CVD. Because of the short half-life of 2.5 mg doses, rivaroxaban needs to be administered twice daily in patients with CVD to ensure that a therapeutic effect is maintained throughout the day.

The benefit of DPI using the COMPASS regimen has been demonstrated in patients with a recent ACS, patients with chronic CAD or PAD, and in patients with lower extremity symptomatic PAD.<sup>25,29–32</sup> So far, rivaroxaban is the only anticoagulant shown to be effective in combination with antiplatelet therapies in these settings.

Studies with other anticoagulants in combination with antiplatelet agents have not yet found a “sweet spot” where there is clinical benefit without an unacceptable risk of bleeding. Rivaroxaban and apixaban have divergent effects on the kinetics of prothrombinase inhibition and suppression of thrombin generation suggesting that dosing regimens will not be interchangeable.<sup>90</sup> Without more data, therefore, rivaroxaban is currently the only oral factor Xa inhibitor that can be used as part of the DPI strategy.

Recent preclinical data reveal a potential role of factor Xa in PAR-mediated disease processes of the vessel wall and demonstrate potential benefits of factor Xa inhibition with rivaroxaban.<sup>91,92</sup> The clinical relevance of these findings requires further investigation to broaden the indications for vascular protection with the DPI strategy.

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